



# Pinpointing regional surface distortions of the amygdala in patients with spider phobia

Melanie S. FISLER<sup>1†</sup>, Andrea Federspiel<sup>1†</sup>, Helge Horn<sup>1</sup>, Thomas Dierks<sup>1</sup>, Wolfgang Schmitt<sup>1</sup>, Roland Wiest<sup>2</sup>, Dominique J-F de Quervain<sup>3</sup> and Leila M. Soravia<sup>1</sup>

\*Correspondence: [federspiel@puk.unibe.ch](mailto:federspiel@puk.unibe.ch)



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<sup>†</sup>These authors contributed equally to this work.

<sup>1</sup>Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Switzerland.

<sup>2</sup>Diagnostic and Interventional Neuroradiology, Inselspital and University of Bern, Switzerland.

<sup>3</sup>Division of Cognitive Neuroscience, Faculty of Medicine and Faculty of Psychology, University of Basel, Switzerland.

## Abstract

The amygdala is a key brain structure involved in emotional processing, especially fear. Neuroimaging studies in patients with phobias have revealed alterations in amygdala reactivity and volumes. Here, we investigated the shape composition of the amygdalae to explore if patients with spider phobia show local morphological differences as compared to healthy controls. Magnetic resonance imaging data was analyzed from 20 female spider phobic patients and 20 age-matched healthy controls. Amygdala shape was quantified using a surface-based mesh modeling method (FIRST). Differences in amygdala topography were most prominently located over the basolateral and central nuclei of the left, but not right amygdala. These differences were further related to the severity of spider phobic symptoms and were independent of age, years of education or duration of illness. The present results point to focal amygdala distortions in spider phobic patients. Due to anomalies within the amygdala, spider phobia might be characterized by a deregulation in both an initial amplified fear response during exposure to spiders as well as a subsequent impaired down-regulation of the elicited fear response.

**Keywords:** Spider phobia, amygdala, shape, volume

## Introduction

Spider phobia is a disease characterized by abnormal and automated fear reaction towards spiders [3]. Theories about the etiology of phobic fear suggest that the enhanced fear response in phobic patients results from a systematically biased interpretation of the danger associated with the feared stimulus [5]. Öhman's theory presumes that in healthy subjects, after encountering a phobia-relevant stimulus, an affective response is elicited through automatic and rapid evaluation of the stimulus, which initiates a sequence of controlled processing procedures. In phobic patients, these controlled mechanisms are suggested to be overridden by the automatic and exaggerated affective response [34].

Indeed, deregulation of emotional processes is one of the core clinical characteristics of spider phobia [16,23] and several neurobiological studies have suggested that the pathophysiology of spider phobia involves brain circuits sub-serving emotion regulation processes, encompassing fronto-limbic brain regions [24,42]. Amongst them, the amygdala has been suggested to play a role in a wide range of emotional processes which include: the perception and experience of emotional states, emotional learning and formation of emotional memories and emotion regulation [4,7,15,22,48,53,63].

Studies on amygdala morphology have revealed that the amygdala complex is not a homogenous structure and comprises sub-groups of specialized nuclei: a) the cortico-medial group with the cortical and medial nuclei, b) the central nucleus, and c) the basolateral group with the accessory basal, basal and lateral nuclei [2,31,32]. The amygdala is presumed to be implicated in the processing of sensory information through extensive connections that receive inputs from several brain areas [32]. Although the functional specialization of the amygdaloid nuclei in humans remains vague, evidence from animal studies suggest distinctive roles of different amygdaloid nuclei, with for example the central nucleus playing a crucial role in reflexive, conditioned responses to aversive stimuli and the basolateral complex playing a key role in voluntary behavior based on emotional episodes [25]. Furthermore, it has been suggested that the basolateral complex of the amygdala plays a key role in mediating the memory-enhancing effect of emotional arousal [44]. However, although animal studies are useful to identify the role of different amygdala nuclei in fear processes, it may not be applicable to humans [28].

Although specific phobias are one of the most prevalent mental disorders in the general population [1,55], it has received limited attention in structural brain imaging, so far. It has been

argued that not only disturbances in amygdala function, but also in its structure might contribute to emotional dysfunction in individuals with anxiety disorders [11,21,47,50]. Though there is extensive literature on differences of amygdala activation in fear and phobias [6,9,13,56,62], to our knowledge, there is no study published on amygdala surface properties in specific phobia. We decided to compare the amygdala shape composition, because volumetric analyses do not account for the different amygdala subdivisions and thus not showing in which part changes are occurring. If only the total volume of the amygdala is estimated, it cannot be determined whether potential volume differences are diffuse and covering the whole amygdala or whether it is localized to specific regions. Since the amygdala has been shown to be an important structure in the generation of fear reactions and consists of several specialized nuclei, the aim of this study was to advance the knowledge about anatomical differences within the amygdala of phobic patients by focusing on differences in surface constitution compared to healthy controls.

## Methods

### Subjects

Participants were recruited by advertisements and were screened by a structured interview to exclude history of psychiatric or neurological illness. Age in the control group was matched with those in the patient group. Only women (in whom specific phobias are much more prevalent [19]) were included into the analysis in order to reduce variation due to gender effects. Because participant's handedness might influence the lateralization or symmetry of the amygdalae [57], only right-handed participants (assessed by the Edinburgh Handedness Inventory [35]) were included into the study. The often-observed co-morbidities make it difficult to directly attribute structural abnormalities to the disease. Therefore, participants were excluded from the study for the following reasons: a) any neurological problem, b) psychiatric diseases, other than spider phobia in patients, and c) medical conditions that could influence the results of the study. We further excluded participants that were taking any medication acting on the cerebral nervous system or using hormonal contraceptives. Written informed consent was obtained from all participants prior to the investigation. Finally, twenty spider phobic patients and twenty healthy controls were entered into the analysis. The study was conducted in accordance with the principles of the Declaration of Helsinki [41] and approved by the ethics committee of the Canton of Bern, Switzerland (161/07).

### Clinical assessment

Diagnosis of spider phobic disease in patients was made according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [3], using a computer-based structured clinical interview (DIA-X) [65], which is based on the Composite International Diagnostic Interview (CIDI) [45]. Asking patients retrospectively about the first appearance of

phobic symptoms assessed information about age at onset of the illness. The duration of illness was defined as the time between onset of spider phobic symptoms and scan acquisition. Patients were screened with a questionnaire for DSM-IV disorders (SKID II) [20] and healthy controls were screened by the Symptom Checklist by Degoratis (SCL-90-R) [18]. In all participants, spider phobic symptoms were assessed more specifically with the Spider Phobia Questionnaire (SPQ) [27] and the Fear of Spiders Questionnaire (FSQ) [58].

### Data acquisition

Structural magnetic resonance images were collected on a 3T Siemens Magnetom Trio Scanner (Erlangen, Germany). T1-weighted structural scans for subcortical analysis were acquired using modified driven equilibrium Fourier transform (mdeft) sequence [12] with the following parameters: repetition time (TR)=7.92msec, echo time (TE)=2,48msec, field of view (FOV)=256x256mm, voxel size=1x1x1mm and 910msec inversion time (Ti) for an optimal contrast-to-noise ratio [12].

### Amygdala shape analysis

Automated amygdala segmentation and vertex analysis were performed using the FIRST module of FSL (FSL v4.1.9; available on: <http://www.fmrib.ox.ac.uk/fsl>). FIRST is an automatic, surface based segmentation tool that is used to analyze shape differences of subcortical brain structures [37]. First, the structural images were brain extracted using BET (brain extraction tool, [51]) and then registered to the MNI152 standard space using global affine transformation. The registration was then refined using a subcortical mask to improve the joint alignment of the subjects' amygdalae. Afterwards, a deformable model was fitted to the images in native space, based on a Bayesian shape and appearance model. The model is derived using a training set consisting of 336 brain scan training set and was then transferred to standard space using affine registration. The shapes of the amygdalae are then expressed as a mean with modes of variation (principal components). Finally, a boundary correction was used to determine which boundary voxels belonged to the amygdala [52]. To determine these voxels, the algorithm requires the number of iterations as input, which was set to 80, according to the recommendations of Patenaude and his colleagues [37]. For more technical details on subcortical segmentation with FIRST, see Patenaude's Thesis [36].

To test for local shape differences between groups, a vertex-wise analysis was finally performed in standard space in order to account for differences in brain size. The statistics were calculated using general linear model (GLM) and corrected for multiple comparisons using false discovery rate (FDR). To test for local shape differences between groups, a vertex-wise analysis was finally performed in standard space in order to account for differences in brain size. More in detail, in a vertex-wise analysis a single vertex point (sing-Vtx) [that describes a scalar in a 3D topological space] is compared to a "reference"

vertex point of a template (temp-Vtx). In this step, vertex points belonging to each separated set of amygdala of each subject are projected onto the surface of a template. A distance between these two points is subsequently estimated. If the resulted distance is positive then the sing-Vtx lays outside the surface of the template; if the resulted distance is negative then the sing-Vtx lays inside the surface of the template.

To clarify whether the severity of the disease or the disease duration has an effect on specific amygdala nuclei, separate correlation analyses were performed within the patient group.

## Statistical analyses

Statistical analyses of clinical scores and demographics were conducted using R (version 2.14.1, <http://www.r-project.org>). Group differences in demographic and clinical characteristics were analyzed with unpaired t-tests. All tests were two-tailed and a probability of less than 0.05 was considered significant.

## Results

### Subject characteristics

As seen in [Table 1](#), spider phobic patients and healthy controls differed significantly in clinical scores with regard to spider phobic symptoms. The two groups did not differ significantly with respect to demographic variables and other clinical scores, except the number of years of education ( $t_{38}=2.48$ ;  $p=0.02$ ). To rule out this potential confound, a separate vertex analysis with level of education as covariate was conducted.

**Table 1. Demographic and clinical characteristics of the patients and their control group.**

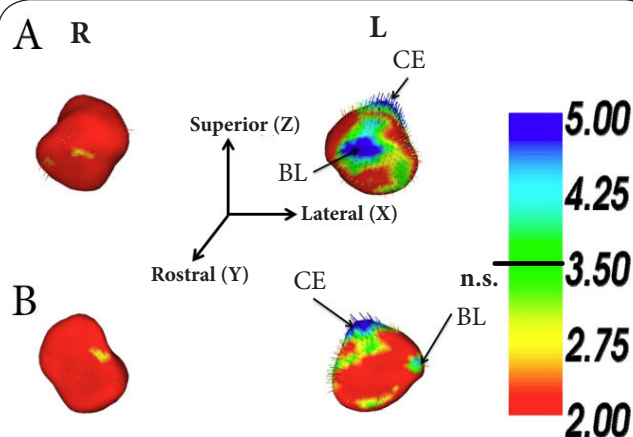
Characteristics	Patients (n=20)		Controls (n=20)		t	p
	Mean	SD	Mean	SD		
Age	29.9	11.3	27.1	5.9	-0.98	0.33
Years of education	13.1	1.9	14.6	2.0	2.47	0.02
Age at onset	6.7	3.3	--	--	--	--
Duration of illness (years)	22.2	13.01	--	--	--	--
Handedness scores	9.7	0.6	9.8	0.4	0.65	0.52
SPQ	21.6	4.3	6.1	3.8	-11.99	0.00
FSQ	79.7	11.6	14.7	18.9	-12.55	0.00

SPQ: Spider Phobia Questionnaire; FSQ: Fear of Spiders Questionnaire

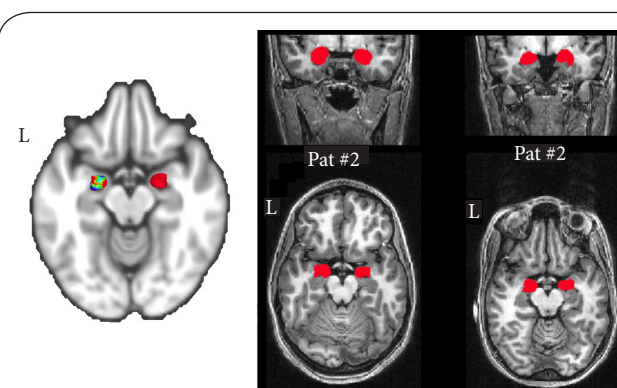
### Amygdala surface properties

In [Figure 1](#), statistical multivariate F statistic maps based on Pillai's Trace indicate regions of structural differences in spider phobic patients relative to healthy controls, with high F-values indicating regions of considerable structural differences. The F-values are color-coded from 2 to 5 with significant differences shown as green/blue and red regions indicating no statistical significance. Surface deformations were restricted to regions in the approximate vicinity of the basolateral complex and the central nucleus of the left amygdala. There were no significant surface differences of the right amygdala between patients and controls.

In order to facilitate the view of these results the shape of the bilateral amygdala are overlaid and projected onto an axial slice of the standard space ([Figure 2](#)). In the same [Figure 2](#) the quality of the segmentation performed by FSL/FIRST is displayed for two representative patients. The anatomical location of the amygdala is shown on an axial slice of these patients that



**Figure 1.** Amygdala statistical maps with F-values indicating structural differences between individuals diagnosed with spider phobia and healthy controls rendered on reference amygdalae. The colors indicate the statistical strength of the difference. Regions in blue/green correspond to the parts of the amygdala that are larger in controls than in patients. The color bar on the right indicates the vertex-wise F-statistic values, corrected for multiple comparisons by False Discovery Rate. (A) ventral view; (B) dorsal view; CE: central nucleus; BL:basolateral complex encompassing the accessory basal, basal and lateral nuclei. The little arrows pointing outwards in the figure indicates increased shape in controls as compared to a template. The level of significance is indicated by a line in the colorbar.



**Figure 2.** Projection of the surface as shown on [Figure 1](#) on a axial slice of the standard brain. The quality of the segmentation performed by FSL/FIRST is displayed for two representative patients. The anatomical location of the amygdala is shown on an axial slice of these patients that also includes the filled contour of the segmentation (in red).



also includes the filled contour of the segmentation (in red). The regions of the amygdala that are larger in controls as compared to patients (see **Figure 1**) were additionally found to lie outside the reference amygdala (i.e., template). This finding is represented on **Figure 1** by the little arrows pointing outwards. The differences in the shape of the amygdala between patients and controls can additionally be expressed as changes in the volume of the amygdala. Patients showed significant smaller left amygdala volumes as compared to controls (Left Amygdala controls: volume=1802.6±162.1 and pat: volume=1649.7±198.9;  $t_{38}=2.66$ ;  $p=0.01$ ). No significant differences were observed for the right amygdala (Right Amygdala controls: volume=1708.8±235.2 and pat: volume=1654.0±374.4;  $t_{38}=0.58$ ;  $p=n.s.$ ). Unfortunately, it is not possible to further delineate the segmentation results to the nuclei level.

### Effect of age, symptom severity and duration of illness

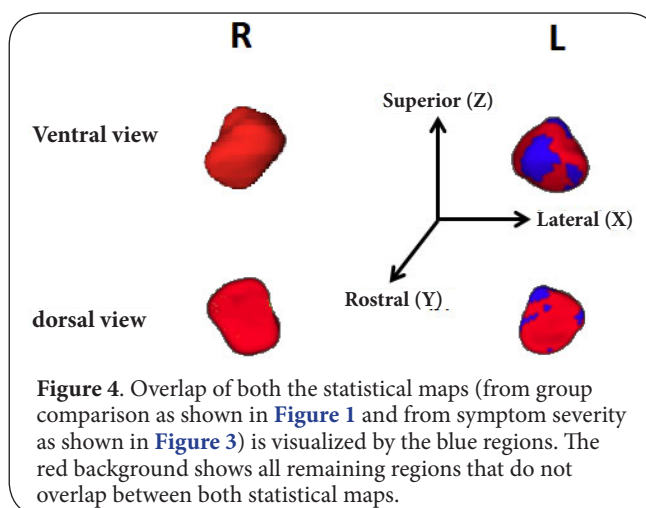
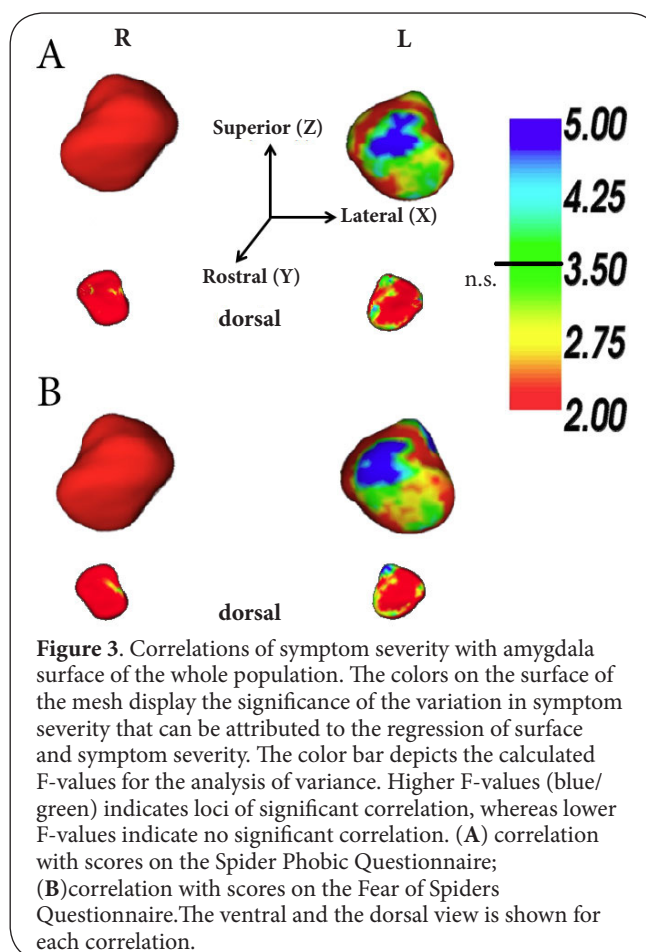
To rule out potential factors that could affect the amygdala surface constitution, correlational analysis between surface-based mesh modeling and age, SPQ score, FSQ score and duration of illness were conducted. Within the whole population, regional differences in the vicinity of the basolateral and central nucleus of the left but not right amygdala significantly correlated with the severity of phobic symptoms (**Figure 3**). Age did not account for differences in amygdala shape in both the patient and control groups. Within the phobic sample, duration of illness was not associated with the surface constitution of both amygdalae.

The overlap of both the statistical maps (from group comparison as shown in **Figure 1** and from symptom severity correlation as shown in **Figure 3**) is visualized on **Figure 4** by the blue regions. The red background shows all remaining regions that do not overlap between both statistical maps. This overlap was constructed by logical conjunction (i.e., AND) of  $p<0.05$  values in both statistical maps. The total number of vertex-points of the overlapping region is 159 out of 229 vertex points in the group comparison and 202 in the correlation analysis.

### Discussion

We evaluated shape differences of the amygdala between patients diagnosed with spider phobia and healthy comparison subjects. The current study demonstrates decrements localized in regions in the vicinity of the basolateral and central nuclei in patients with spider phobia. These sub-regional alterations were associated with symptom severity. Moreover, results could not be attributed to years of education nor age or duration of illness. Therefore, the observed differences in left amygdala topography over distinct nuclei in our patient group might be linked to disorder-related amplified fear responses during phobic situations.

Theories about the etiology of phobic fear suggested that laterality differences may account for innate versus conditioned



fearful stimuli, with the left amygdala playing a greater role in response to innate fearfully stimuli such as spiders [14]. Evidence for this hypothesis stems from neuroimaging studies investigating the habituation phenomenon which demonstrated greater and more sustained activation of the

left amygdale [39,64,66]. In patients, the observed structural differences in the left amygdala could reflect impairments in top-down cognitively mediated processing. Our findings of left-lateralized differences suggest that the two amygdalae do not perform entirely equivalent functions. Evidence from a functional imaging study suggest, that activation of the left amygdala is strongly correlated with the fear response [38]. Hence, the right amygdala may have a general role during the initial automatic reaction, whereas the left amygdala could be more specifically involved in a more differentiated emotional reaction [33,66].

Apart the lateralization of fear responses, animal studies suggest that the basolateral nucleus is critically involved in fear memory [17,43] or in the consolidation of information that leads to phobic avoidance and constitutes a genetic predisposition to acquire specific phobias [25]. Because the amygdala integrates the information related to fear and strong emotions and sends outputs via the central nucleus for automatic arousal and via the basolateral nucleus for more active aspects of coping [29], atrophies in these regions may lead to phobic diseases. Importantly, the central nucleus have been suggested to be involved in many of the phobic symptoms and may exert modulatory influences upon hypothalamus and brainstem, mediating autonomic reactions which are characteristic of fear behavior [8,10,30,40].

Beyond animal studies, Sheline and colleagues [49] found a decrease in the size of both basolateral nuclei in patients with depression, attributing these volume losses to neuronal degeneration as a result of hypercortisolemia which may occur by the amplified activity of the amygdala. In phobic patients, the hyperactivity of the amygdala has been proposed to result from a lack of cortical inhibition by the prefrontal cortex, which sends dense projections to the amygdala primarily through GABAergic neurons [54]. The basal nucleus of the amygdala receives inputs from the hippocampus and prefrontal cortex and might integrate these signals to regulate the fear response [32,61]. Thus, there might occur an uncoupling of prefrontal inhibition of the amygdala in phobic patients that triggers extreme amygdala responses. Though, this uncoupling might be further supported by the observed structural deficits within the amygdala.

Altogether, it is still unclear whether morphological alterations of the amygdala constitute a state characteristic of the disorder or a trait marker. Multiple mechanisms could account for the occurrence of behavioral symptoms, functional differences and morphological features. The interplays between these factors are largely unknown. Though, phobic diseases could be driven by a genetic polymorphisms x environment interaction, modulated by molecular processes that lead to the expression of adaptive changes and phobic diseases. Furthermore, the microstructural determinants of group differences in amygdala morphology are unknown, as is the extent to which differences in surface properties relate to abnormalities in the underlying nuclei of the amygdala.

It is not trivial to provide a conclusive meaning of what the measure of surface morphology generally captures. Intuitively, the measure of shape morphology as compared to a simple volumetric investigation offers a more detailed view of the investigated region of interest. In fact, volumetric changes alone could result from two totally different regions that share no or few geometrical properties (i.e., like a sphere and a cube; or a cube and a torus). Shape analysis additionally provides a micro-architectonic description of local deviations of a region of interest from a template. In the present study both, the volume and the shape of the left amygdala were found to be significant different in patients as compared to healthy controls. The measure of volume alone represents just a simple number while the shape analysis additionally provides detailed information on how and where the surface of the amygdala might be deformed. The assessment of deformation can be understood as a non-linear method that may capture morphological changes and that goes beyond conventional linear voxel wise analysis of volume. Moreover, volume changes in the left amygdala alone describe uniquely a global feature while shape analysis additionally captures regional properties within the left amygdala. The observed volumetric changes in the patients left amygdala are not due to a general reduction in volume as compared to healthy controls: shape analysis locates the significant deviations in distinct nuclei of the left amygdala. This is the major insight that in the present study was uniquely obtained through the shape analysis.

Nonetheless, there are a few studies investigating morphological properties such as in hippocampal and entorhinal cortex of elderly [60], mild cognitive impairment and Alzheimer's disease [59] and hippocampal gender differences in puberty [46]. All these investigations are based on FSL/FIRST as described in [37].

There are some limitations of the study that need to be taken into account. Focusing only on single brain regions does not recognize that phobia is a disorder encompassing multiple brain regions sub-serving phobic fear. Furthermore, the standard resolution of structural imaging at 3T does not allow a reliable localization of structural alterations within specific amygdala cell groups. The relative sensitivity of magnetic resonance imaging in detecting amygdala damage, compared to histological analysis has so far not been established. The precise identification of amygdala nuclei requires histological investigation. It needs to be clarified that the labeling of the amygdala nuclei in this study was based on information obtained from a brain atlas [31]. Furthermore, the possibility remains that surface distortions also reflect atrophies in nuclei that are not represented on the surface of the amygdala. The modest number of subjects in each group (n=20) raises the possibility of a type II statistical error. Moreover, sex differences may also have an influence on amygdala structure [26]. As we only analyzed data from females, results can't be generalized.

Overall, the findings provide initial evidence for structural

amygdala abnormalities as an element in the pathophysiology of phobic diseases. Our findings further illuminate the need to treat the amygdala as a heterogeneous structure. The documented findings might be clinically relevant as localized alterations might be reversible by pharmacotherapy or psychotherapy, which should be addressed in future studies. Although future prospective longitudinal research is required to establish structure-function relationship and neural mechanisms underlying phobic diseases, this study highlights the importance of the amygdala as a potentially important neural substrate.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

Authors' contributions	AF	MSF	HS	TD	WS	RW	DJD	LMS
Research concept and design	--	--	--	--	--	--	✓	✓
Collection and/or assembly of data	--	✓	--	--	--	--	--	--
Data analysis and interpretation	--	✓	--	--	--	--	--	--
Writing the article	✓	✓	--	--	--	--	--	--
Critical revision of the article	✓	✓	✓	✓	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓	✓	✓	✓	✓
Statistical analysis	--	✓	--	--	--	--	--	--

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### References

- Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I and Haro JM. **Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project.** *Acta Psychiatr Scand Suppl.* 2004; **109**:21-7. | [Article](#) | [PubMed](#)
- Amaral DG and Insausti R. **Retrograde transport of D-[3H]-aspartate injected into the monkey amygdaloid complex.** *Exp Brain Res.* 1992; **88**:375-88. | [Article](#) | [PubMed](#)
- Association AP. **Diagnostic and statistical manual of mental disorders. 4th edition** (DSM-IV) edn, Washington. 1994.
- Baxter MG and Murray EA. **The amygdala and reward.** *Nat Rev Neurosci.* 2002; **3**:563-73. | [Article](#) | [PubMed](#)
- Beck AT, Emery G and Greenberg RL. **Anxiety disorders and phobias: A cognitive perspective.** New York, NY, US: Basic Books. 2005.
- Carlsson K, Petersson KM, Lundqvist D, Karlsson A, Ingvar M and Ohman A. **Fear and the amygdala: manipulation of awareness generates differential cerebral responses to phobic and fear-relevant (but nonfeared) stimuli.** *Emotion.* 2004; **4**:340-53. | [Article](#) | [PubMed](#)
- Costafreda SG, Brammer MJ, David AS and Fu CH. **Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies.** *Brain Res Rev.* 2008; **58**:57-70. | [Article](#) | [PubMed](#)
- Davis M. **The role of the amygdala in fear-potentiated startle: implications for animal models of anxiety.** *Trends Pharmacol Sci.* 1992; **13**:35-41. | [Article](#) | [PubMed](#)
- Davis M. **The role of the amygdala in fear and anxiety.** *Annu Rev Neurosci.* 1992; **15**:353-75. | [Article](#) | [PubMed](#)
- Davis M. **Neurobiology of fear responses: the role of the amygdala.** *J Neuropsychiatry Clin Neurosci.* 1997; **9**:382-402. | [Pdf](#) | [PubMed](#)
- De Bellis MD, Casey BJ, Dahl RE, Birmaher B, Williamson DE, Thomas KM, Axelson DA, Frustaci K, Boring AM, Hall J and Ryan ND. **A pilot study of amygdala volumes in pediatric generalized anxiety disorder.** *Biol Psychiatry.* 2000; **48**:51-7. | [Article](#) | [PubMed](#)
- Deichmann R, Schwarzbauer C and Turner R. **Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3 T.** *Neuroimage.* 2004; **21**:757-67. | [Article](#) | [PubMed](#)
- Dilger S, Straube T, Mentzel HJ, Fitzek C, Reichenbach JR, Hecht H, Krieschel S, Gutberlet I and Miltner WH. **Brain activation to phobia-related pictures in spider phobic humans: an event-related functional magnetic resonance imaging study.** *Neurosci Lett.* 2003; **348**:29-32. | [Article](#) | [PubMed](#)
- Dolan RJ and Morris JS. **The functional anatomy of innate and acquired fear: Perspectives from neuroimaging.** In: *Cognitive neuroscience of emotion.* Series in affective science. New York, NY, US: Oxford University Press. 2000; 225-241. | [Article](#)
- Drevets WC. **Neuroimaging abnormalities in the amygdala in mood disorders.** *Ann N Y Acad Sci.* 2003; **985**:420-44. | [Article](#) | [PubMed](#)
- Etkin A and Wager TD. **Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia.** *Am J Psychiatry.* 2007; **164**:1476-88. | [Article](#) | [PubMed](#) | [Abstract](#) | [PubMed Full Text](#)
- Fanselow MS and LeDoux JE. **Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala.** *Neuron.* 1999; **23**:229-32. | [Article](#) | [PubMed](#)
- Frank G and Stacker KH. **Reliability and validity of the Symptom Checklist (SCL-90-R, Derogatis, 1986) in standardized versus homogenous item-blocked sequence.** *Diagnostica.* 1995; **41**:349-373.
- Fredrikson M, Annas P, Fischer H and Wik G. **Gender and age differences in the prevalence of specific fears and phobias.** *Behav Res Ther.* 1996; **34**:33-9. | [Article](#) | [PubMed](#)
- Fydrich T, Renneberg B, Schmitz B., Wittchen, H.-U. **SKID-II : Strukturiertes Klinisches Interview für DSM-IV, Achse II: Persönlichkeitsstörungen.** Göttingen: Hogrefe. 1997.
- Goossens L, Snaert S, Peeters R, Griez EJ and Schruers KR. **Amygdala hyperfunction in phobic fear normalizes after exposure.** *Biol Psychiatry.* 2007; **62**:1119-25. | [Article](#) | [PubMed](#)
- Hare TA, Tottenham N, Davidson MC, Glover GH and Casey BJ. **Contributions of amygdala and striatal activity in emotion regulation.** *Biol Psychiatry.* 2005; **57**:624-32. | [Article](#) | [PubMed](#)
- Hermann A, Schafer A, Walter B, Stark R, Vaitl D and Schienle A. **Emotion regulation in spider phobia: role of the medial prefrontal cortex.** *Soc Cogn Affect Neurosci.* 2009; **4**:257-67. | [Article](#) | [PubMed](#) | [Abstract](#) | [PubMed Full Text](#)
- Johanson A, Gustafson L, Passant U, Risberg J, Smith G, Warkentin S and Tucker D. **Brain function in spider phobia.** *Psychiatry Res.* 1998; **84**:101-11. | [Article](#) | [PubMed](#)
- Killcross S, Robbins TW and Everitt BJ. **Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala.** *Nature.* 1997; **388**:377-80. | [Article](#) | [PubMed](#)
- Kim HJ, Kim N, Kim S, Hong S, Park K, Lim S, Park JM, Na B, Chae Y, Lee J, Yeo S, Choe IH, Cho SY and Cho G. **Sex differences in amygdala subregions: evidence from subregional shape analysis.** *Neuroimage.* 2012; **60**:2054-61. | [Article](#) | [PubMed](#)
- Klorman R, Weerts TC, Hastings JE, Melamed BG and Lang PJ. **Psychometric description of some specific-fear questionnaires.** *Behavior Therapy.* 1974; **5**:401-409. | [Article](#)
- LeDoux J. **The emotional brain, fear, and the amygdala.** *Cell Mol*



- Neurobiol.* 2003; **23**:727-38. | [Article](#) | [PubMed](#)
29. LeDoux JE. **Emotion circuits in the brain.** *Annu Rev Neurosci.* 2000; **23**:155-84. | [Article](#) | [PubMed](#)
30. Liu X, Wellman LL, Yang L, Ambrozewicz MA, Tang X and Sanford LD. **Antagonizing corticotropin-releasing factor in the central nucleus of the amygdala attenuates fear-induced reductions in sleep but not freezing.** *Sleep.* 2011; **34**:1539-49. | [Article](#) | [PubMed Abstract](#) | [PubMed Full Text](#)
31. Mai JK, Assheuer J and Paxinos G. **Atlas of the Human Brain.** Academic Press, San Diego. 1997.
32. McDonald AJ. **Cortical pathways to the mammalian amygdala.** *Prog Neurobiol.* 1998; **55**:257-332. | [Article](#) | [PubMed](#)
33. Morris JS, Ohman A and Dolan RJ. **Conscious and unconscious emotional learning in the human amygdala.** *Nature.* 1998; **393**:467-70. | [Article](#) | [PubMed](#)
34. Ohman A. **Face the beast and fear the face: animal and social fears as prototypes for evolutionary analyses of emotion.** *Psychophysiology.* 1986; **23**:123-45. | [Article](#) | [PubMed](#)
35. Oldfield RC. **The assessment and analysis of handedness: the Edinburgh inventory.** *Neuropsychologia.* 1971; **9**:97-113. | [Article](#) | [PubMed](#)
36. Patenaude B. **Bayesian Statistical Models of Shape and Appearance for Subcortical Brain Segmentation.** *University of Oxford, Oxford.* 2007. | [Website](#)
37. Patenaude B, Smith SM, Kennedy DN and Jenkinson M. **A Bayesian model of shape and appearance for subcortical brain segmentation.** *Neuroimage.* 2011; **56**:907-22. | [Article](#) | [PubMed Abstract](#) | [PubMed Full Text](#)
38. Phelps EA, O'Connor KJ, Gatenby JC, Gore JC, Grillon C and Davis M. **Activation of the left amygdala to a cognitive representation of fear.** *Nat Neurosci.* 2001; **4**:437-41. | [Article](#) | [PubMed](#)
39. Phillips ML, Medford N, Young AW, Williams L, Williams SC, Bullmore ET, Gray JA and Brammer MJ. **Time courses of left and right amygdalar responses to fearful facial expressions.** *Hum Brain Mapp.* 2001; **12**:193-202. | [Article](#) | [PubMed](#)
40. Phillips RG and LeDoux JE. **Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning.** *Behav Neurosci.* 1992; **106**:274-85. | [Pdf](#) | [PubMed](#)
41. Rickham PP. **Human Experimentation. Code of Ethics of the World Medical Association. Declaration of Helsinki.** *Br Med J.* 1964; **2**:177. | [PubMed Abstract](#) | [PubMed Full Text](#)
42. Roffman JL, Marci CD, Glick DM, Dougherty DD and Rauch SL. **Neuroimaging and the functional neuroanatomy of psychotherapy.** *Psychol Med.* 2005; **35**:1385-98. | [Article](#) | [PubMed](#)
43. Roozendaal B, McEwen BS and Chattarji S. **Stress, memory and the amygdala.** *Nat Rev Neurosci.* 2009; **10**:423-33. | [Article](#) | [PubMed](#)
44. Roozendaal B and McGaugh JL. **Basolateral amygdala lesions block the memory-enhancing effect of glucocorticoid administration in the dorsal hippocampus of rats.** *Eur J Neurosci.* 1997; **9**:76-83. | [Article](#) | [PubMed](#)
45. Rubio-Stipec M, Bravo M and Canino G. **[The Composite International Diagnostic Interview (CIDI): an epidemiologic instrument suitable for using in conjunction with different diagnostic systems in different cultures].** *Acta Psiquiatr Psicol Am Lat.* 1991; **37**:191-204. | [Article](#) | [PubMed](#)
46. Satterthwaite TD, Vandekar S, Wolf DH, Ruparel K, Roalf DR, Jackson C, Elliott MA, Bilker WB, Calkins ME, Prabhakaran K, Davatzikos C, Hakonarson H, Gur RE and Gur RC. **Sex differences in the effect of puberty on hippocampal morphology.** *J Am Acad Child Adolesc Psychiatry.* 2014; **53**:341-350 e1. | [Article](#) | [PubMed](#)
47. Sehlmeier C, Dannlowski U, Schoning S, Kugel H, Pyka M, Pfeleiderer B, Zwitterlood P, Schiffbauer H, Heindel W, Arolt V and Konrad C. **Neural correlates of trait anxiety in fear extinction.** *Psychol Med.* 2011; **41**:789-98. | [Article](#) | [PubMed](#)
48. Sergerie K, Chochol C and Armony JL. **The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies.** *Neurosci Biobehav Rev.* 2008; **32**:811-30. | [Article](#) | [PubMed](#)
49. Sheline YI, Gado MH and Price JL. **Amygdala core nuclei volumes are decreased in recurrent major depression.** *Neuroreport.* 1998; **9**:2023-8. | [Article](#) | [PubMed](#)
50. Shioiri T. **[Neuroimaging and pathology in anxiety disorders, especially stress-induced fear circuitry disorders].** *Nihon Shinkei Seishin Yakurigaku Zasshi.* 2010; **30**:135-9. | [Article](#) | [PubMed](#)
51. Smith SM. **Fast robust automated brain extraction.** *Hum Brain Mapp.* 2002; **17**:143-55. | [Article](#) | [PubMed](#)
52. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM and Matthews PM. **Advances in functional and structural MR image analysis and implementation as FSL.** *Neuroimage.* 2004; **23** Suppl 1:S208-19. | [Article](#) | [PubMed](#)
53. Soares JC and Mann JJ. **The anatomy of mood disorders--review of structural neuroimaging studies.** *Biol Psychiatry.* 1997; **41**:86-106. | [Article](#) | [PubMed](#)
54. Sotres-Bayon F, Bush DE and LeDoux JE. **Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction.** *Learn Mem.* 2004; **11**:525-35. | [Article](#) | [PubMed](#)
55. Stinson FS, Dawson DA, Patricia Chou S, Smith S, Goldstein RB, June Ruan W and Grant BF. **The epidemiology of DSM-IV specific phobia in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions.** *Psychol Med.* 2007; **37**:1047-59. | [Article](#) | [PubMed](#)
56. Straube T, Mentzel HJ and Miltner WH. **Neural mechanisms of automatic and direct processing of phobic stimuli in specific phobia.** *Biol Psychiatry.* 2006; **59**:162-70. | [Article](#) | [PubMed](#)
57. Szabo CA, Xiong J, Lancaster JL, Rainey L and Fox P. **Amygdalar and hippocampal volumetry in control participants: differences regarding handedness.** *AJNR Am J Neuroradiol.* 2001; **22**:1342-5. | [Article](#) | [PubMed](#)
58. Szymanski J and O'Donohue W. **Fear of Spiders Questionnaire.** *J Behav Ther Exp Psychiatry.* 1995; **26**:31-4. | [Article](#) | [PubMed](#)
59. Thomann PA, Seidl U, Brinkmann J, Hirjak D, Traeger T, Wolf RC, Essig M and Schroder J. **Hippocampal morphology and autobiographic memory in mild cognitive impairment and Alzheimer's disease.** *Curr Alzheimer Res.* 2012; **9**:507-15. | [Article](#) | [PubMed](#)
60. Thomann PA, Wustenberg T, Nolte HM, Menzel PB, Wolf RC, Essig M and Schroder J. **Hippocampal and entorhinal cortex volume decline in cognitively intact elderly.** *Psychiatry Res.* 2013; **211**:31-6. | [Article](#) | [PubMed](#)
61. Vazdarjanova A and McGaugh JL. **Basolateral amygdala is involved in modulating consolidation of memory for classical fear conditioning.** *J Neurosci.* 1999; **19**:6615-22. | [Article](#) | [PubMed](#)
62. Veltman DJ, Tuinebreijer WE, Winkelman D, Lammertsma AA, Witter MP, Dolan RJ and Emmelkamp PM. **Neurophysiological correlates of habituation during exposure in spider phobia.** *Psychiatry Res.* 2004; **132**:149-58. | [Article](#) | [PubMed](#)
63. Vuilleumier P. **How brains beware: neural mechanisms of emotional attention.** *Trends Cogn Sci.* 2005; **9**:585-94. | [Article](#) | [PubMed](#)
64. Whalen PJ. **Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala.** *Curr Dir Psychol Sci.* 1998; **7**:177-188. | [Article](#)
65. Wittchen HU and Beloch E. **Instruktionsmanual zur Durchführung von DIA-X-Interviews; Diagnostisches Expertensystem für psychische Störungen.** Harcourt Test Services. 1997. | [Website](#)
66. Wright CI, Fischer H, Whalen PJ, McInerney SC, Shin LM and Rauch SL. **Differential prefrontal cortex and amygdala habituation to repeatedly presented emotional stimuli.** *Neuroreport.* 2001; **12**:379-83. | [Article](#) | [PubMed](#)

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